

NATIONAL INSTITUTES OF HEALTH FY 2003 CONGRESSIONAL JUSTIFICATION OVERVIEW

The mission of the National Institutes of Health (NIH) is to expand fundamental knowledge about the nature and behavior of living systems and to improve and develop new strategies for the diagnosis, treatment, and prevention of disease with the goal of improving health. The 27 Institutes and Centers, which comprise the NIH, support research and researchers working in universities, medical centers, hospitals, and research institutions in every State and territory in the Nation and in many countries around the world. The NIH also conducts research in its own laboratories. In order to help ensure that there is a continuing cadre of outstanding scientists for the future and that there are facilities in which to conduct this research, the Agency supports research training, career development, and some buildings and facilities programs.

For each of the past four years, the NIH has received historic increases in its budget and thus remains on course to double its FY 1998 budget by the end of FY 2003. These increases have allowed the NIH to build a broad portfolio of research that provides the foundation for incremental advances and medical breakthroughs. This investment includes funding for basic and clinical research – both important to understanding and solving problems related to specific diseases and public health problems such as cancer and bioterrorism. Funding for these projects includes investigator training, the cost of equipment, supplies, and services such as facility maintenance and information management.

Modern scientists share much in common with explorers of the past. For example, although Lewis and Clark could not plan for what they might find on their journey, they did plan their route and made sure they had the right supplies and a knowledgeable expedition crew before they began. In the same manner, although the outcomes of medical research are often unpredictable, the NIH and its Institutes and Centers plan research both at the project and program level by seeking the advice of scientists, patients, health care payers and providers, the public, the Congress, and the Administration. The goal of such planning and priority setting is to maintain a diverse portfolio of research founded on both public health need and scientific opportunity – opportunity that offers the best prospects for new knowledge, improved diagnostics, effective treatments, innovative prevention strategies, and ultimately, better health.

NIH's future efforts are rooted in knowledge gained over decades of publicly supported medical research. With the increases proposed for FY 2003, NIH will engage in new and expanded efforts in genomics, proteomics, therapeutics, and prevention. FY 2003 funds will also be used to address converging arenas of scientific opportunity and public health, such as bioterrorism, cancer, diabetes, Parkinson's disease, Alzheimer's disease, asthma, and minority health.

Genomics

The Human Genome Project (HGP) has provided biomedical researchers with a vast and unprecedented amount of data. The first draft of the human genome

sequence, completed in 2001, revealed that humans have some 30,000 genes. The final sequence is expected to be completed by 2003, well ahead of schedule.

Although the DNA sequence between any two individuals is 99.9 percent identical, genetic variations hold the key to understanding disease mechanisms. In order to capture this variation and understand its role in disease, the Human Genome Project and its partners are creating a catalog of human single nucleotide polymorphisms (SNPs), which are places along the sequence where the DNA sequence varies by a single base pair or DNA letter. Between two individuals, such variations occur approximately once every 1000 bases. To date, through the combined efforts of NIH and its partners, nearly 3 million SNPs have been identified and are available in public databases. Scientists are now using SNPs to scan the entire genome to find chromosomal regions that are statistically associated with disease. Once such regional variations are identified, scientists can use the working draft of the human genome to narrow their search for the disease-causing alterations. Such “whole-genome association” studies will also be used to develop novel diagnostics and drugs that are tailored to patients' genetic profiles.

It is also important to understand the pattern of genetic variations across populations, a so-called “haplotype map.” The SNP variants do not occur at random. By finding the pattern of variation along chromosomes, scientists can begin to select the set of SNPs that represents nearly all of the underlying pattern of variation. The availability of such haplotype maps will thus make finding disease genes faster, more efficient, more comprehensive, and much more affordable. To this end, the NIH brought together the world's leading experts to discuss how best to develop haplotype maps. This group is working to design a project that focuses on mapping genes that contribute to disease. The group also is making plans to develop methods for constructing such maps and to gather data about haplotype structure in populations. They are also determining the types of populations and samples to be included, outlining the relevant ethical issues to be considered and exploring how such a project should be organized.

With the increasing pace of new developments in biomedical research, biomedical applications of information technology, more sophisticated mathematical models, computer programs, and data storage systems are being developed. NIH is ensuring that the Nation's biomedical research enterprise has the trained professionals it needs in computational biology, including mathematical modeling in the life sciences, advanced imaging, and molecular biology. For example, the NIH is playing a lead role in the evolving field of bioinformatics, which covers a wide range of disciplines, including computer science, biology, physiology, and probability/statistics. To this end, NIH launched the Biomedical Information Science and Technology Initiative (BISTI), which resulted in the establishment of National Programs of Excellence in Biomedical Computing; the Information Storage, Curation, Analysis, and Retrieval grants to institutions to train people in these areas of science; and a joint NIH/National Science Foundation program to support research in mathematical biology.

Proteomics

The ultimate goal of sequencing the human genome is to understand the root causes of, and to find effective treatments for, diseases. This requires a fundamental understanding of the proteins expressed by each gene and the roles such proteins play in all biological processes. Proteins, which are made up of amino acids, are the building blocks of the cells and tissues of the body and control virtually all biological function. "Proteomics" is the simultaneous study of a large number of proteins or the complete set of an organism's proteins (its "proteome"). It is an area of research in which investigators separate, identify, and characterize proteins to better understand their functions and the regulation of their functions.

To this end, NIH has undertaken the Protein Structure Initiative to determine the three-dimensional structures of all proteins in nature by using the technique X-ray crystallography. For example, understanding how proteins are made requires detailed knowledge of the enzyme RNA Polymerase II, which is the key enzyme involved in the important first step of making proteins in all organisms – from yeast to humans. After nearly 20 years of effort, structural biologists finally succeeded in using X-ray crystallography to elucidate the three-dimensional structure of RNA Polymerase II. This is giving scientists their first look at the large, multi-unit enzyme in action and how its subunits fit together to form the molecular machine that ultimately leads to the formation of proteins.

The study of protein structures also involves organizing protein sequence databases into "families," targeting each family for direct structure determination, and using this set of structures to model other related proteins with the goal of fully characterizing structure and function relationships and the evolution of protein structures. With the increasing number and variety of both protein sequences and functional information, the research community will become increasingly dependent on the availability of a database of all possible proteins encoded by the genome of an organism to understand how these proteins function in making up a living cell, knowledge that is essential for the mission of NIH. In this regard, in FY 2003 several NIH Institutes are planning to fund a centralized protein sequence database that will include information on protein sequence, nomenclature, and functional information. Importantly, scientists throughout the world will have unrestricted access to the information in this database.

A major obstacle to proteomics is the need for more and better tools, technologies, and database resources to explore protein expression, structure, and function in a high-throughput, low cost manner. NIH is taking an active role in stimulating and funding new proteomics-related technologies. One important area of emphasis is cell labeling. For example, a technique for labeling proteins in cells under different conditions allows for much needed comparisons between cell states before and after administration of a drug, or between a normal cell and a diseased cell. Such labeling techniques can also be used to reveal proteins overproduced or underproduced during the course of, or as the result of, disease. Such proteins are important targets for the design of new, more effective, and less toxic medications.

Another emerging area of analytical technique development is protein chip technology. The ability of these chips to ‘read’ a large number of proteins at once is already having a significant impact on both drug development and clinical diagnosis. It will expedite the discovery of protein markers for diseases and thus targets for new treatments. Ultimately, this technology will not only be able to detect proteins associated with specific stages of diseases, but will be important to prevention, diagnosis, and the development of new therapeutics.

Therapeutics

By using our knowledge about genes, their expressed proteins, and the role they play in disease, future treatments will be based on the underlying causes of disease, rather than its symptoms. Such information will also help classify diseases by subtypes that may respond to different treatments or result in different or varied side effects. For example, as we understand more about how particular proteins fit into disease pathways and cause cell damage, we will be able to use these molecular targets to design specific drugs to block the damage. The approval of the drug Gleevec™ this year for chronic myelogenous leukemia (CML) was the first of the so-called “molecular target” drugs. Gleevec™ was successfully designed to block the signaling pathway of the BCR-ABL protein, which causes uncontrolled cell division. Thus, Gleevec™ destroys cancerous cells while healthy cells remain unaffected. To date, the indiscriminate destruction of cells, both cancerous and healthy, has been a significant drawback of chemotherapy drugs. As functions of more proteins involved in diseases are uncovered, more “molecular target” drugs like Gleevec™ can be developed.

The development of new or improved instruments and technologies also plays a critical role in the success of therapeutic development. The dawn of the 21st century finds biomedical research increasingly more complex and requiring a more multi-disciplinary approach to problem solving. New knowledge often reveals underlying complexities about normal and abnormal processes that have not been previously understood. For example, NIH is initiating the Radiation Modifier Evaluation Module Program, which seeks to integrate molecular imaging, molecular signatures, and molecular therapeutics with radiation therapy. It aids NIH investigators, as well as researchers in industry, in the design and development of treatments using novel molecular, biologic, and cytotoxic agents in conjunction with radiation therapy. Similarly, the Molecular Targets Laboratory focuses on developing a resource for collaboration between chemists and biologists to produce libraries of potential anti-cancer compounds for public distribution, developing screening assays suitable for high-throughput screening of chemical libraries of potential agents, and confirming a drug’s initial ability to alter the drug target in cancer cells.

Continued progress in the development of therapeutics also depends on the recruitment and retention of highly qualified health professionals as clinical investigators. In this regard, the NIH plans to expand its Extramural Loan Repayment Program for Clinical Researchers (LRP-CR). The LRP-CR provides for the repayment of the educational loan debt of qualified health professionals who agree to conduct clinical research. The NIH has implemented extramural loan repayment programs to attract new investigators to enter into and remain in careers in biomedical

research. These programs offer educational loan repayment for health professionals, primarily physicians and doctorally prepared research scientists, who agree to conduct clinical research, pediatric research, and minority health disparities research. In addition, there is a program to attract clinical researchers from disadvantaged backgrounds into clinical research. The NIH will continue to fund these programs in fiscal year 2003, and looks to their success as a mechanism to protect and improve public health by attracting health care professionals to careers in biomedical research.

Clinical research remains an essential link in the continuum of biomedical research supported by the NIH. The translation of basic biomedical findings into clinical studies on human subjects and populations helps scientists to develop direct applications for the prevention, diagnosis, treatment and cure of human disease, and assists the Nation with critical health care problems. For example, research on treatments for mental disorders traditionally entails the use of a single treatment modality in a more narrowly defined sample of patients. In practice, however, multiple interventions are typically used in various combinations, based as much on convenience, assumption and guesswork, as on evidence-based medicine. Clinical trials will be developed to study a range of treatment modalities, utilizing combinations of psychopharmacologic agents, and somatic and/or psychosocial interventions, with special focus on mood and anxiety disorders, schizophrenia, and Alzheimer's disease.

Another important clinical research effort deals with the highly active anti-retroviral therapy (HAART), which has dramatically improved the survival of patients with HIV infection. However, these patients can develop a variety of metabolic complications that comprise major risk factors for diabetes and cardiovascular disease, including insulin resistance and abnormalities in distribution of body fat. A new initiative will undertake studies to develop and test novel approaches to treat HAART-associated metabolic complications.

Over fifty percent of the adult U.S. population is overweight and at increased risk of developing cardiovascular disease. A new initiative will promote interactive basic and clinical studies to explain how excessive body weight contributes to the development of cardiovascular disease such as atherosclerosis, enlarged hearts, heart failure and irregular heart beats. The role of adipose tissue in inflammation, the effects of obesity on maturation of the cardiovascular, respiratory and endocrine systems, and the interactions between overweight and conditions such as chronic sleep loss, hypertension and insulin resistance will be illuminated.

Prevention

Research on disease prevention is a major component of the NIH mission. Gains in knowledge on disease risk, prevention, and early detection have resulted in significant advances leading to declines in mortality from infectious diseases and chronic diseases, as well as improved life expectancy and quality of life. In fact, many of today's greatest public health challenges involve diseases that are largely behavior-based and preventable. A great deal remains to be learned about how to motivate people to engage in

healthy behaviors, avoid unhealthy or high-risk behaviors, and maintain their behavior change over a lifetime. Clinical research and epidemiologic studies are also providing new understandings about the physiological links between behavior and disease.

NIH is launching a number of prevention initiatives in FY 2003. For example, the National Drug Abuse Prevention Research Initiative will involve a number of partners working together to test the effectiveness of new and existing science-based prevention approaches in different communities, while simultaneously studying how best to adapt the programs for local communities. Another component of this Initiative will consist of transdisciplinary prevention research centers, which will foster collaborations between neuroscientists, behavioral scientists, cognitive scientists, and drug abuse prevention researchers to address knowledge gap areas and how to approach the scientific questions in drug abuse prevention research in new ways.

In addition to the increasing trend in drug abuse, an equally disturbing trend is the abuse of alcohol on college campuses. Alcohol consumption by college students results in deaths, injuries, crimes, and sexual assaults. It disrupts the lives and studies of students who drink as well as their non-drinking peers and has a negative impact on the college environment and surrounding community. The NIH is undertaking an initiative that will include the first nationally representative, prospective, longitudinal study of drinking among adolescents and college-age youth. Results will provide information about the occurrence, causes, course, and short- and long-term outcomes of alcohol-related problems among adolescents and college students. It also will provide information about factors that appear to lower risk of alcohol problems in this youthful population.

Bioterrorism

The events of September 11, 2001, and the subsequent intentional release of anthrax spores are having a substantial effect on the NIH and the research it supports. As a result of the recent deaths due to inhalation anthrax, thousands of people were placed on antibiotic therapy. It is clear that the NIH has an important role in both conducting research on the agents of bioterrorism and in ensuring that there is up-to-date and accurate information on therapeutic options and other interventions to guide the responses to terrorist attacks.

The NIH has supported research on the most likely agents of bioterrorism (smallpox, anthrax, plague and tularemia) for several years, and much progress has been made during that time, such as the identification of an antiviral drug that can be used to treat infections such as small pox (variola or vaccinia) and the development of a new vaccine to prevent anthrax. The NIH is now ramping up relevant research efforts. The goals of this markedly expanded research effort are to develop the countermeasures (vaccines, therapeutics, and diagnostic tests) that will be needed to respond to and control the intentional or unintentional release of agents of bioterrorism.

The initial focus of this research effort is on the agents identified in the Centers for Disease Control and Prevention threat list – specifically those identified in Category A (smallpox,

anthrax, plague, tularemia, viral hemorrhagic agents and botulism). A major component of this research program is to enhance the Nation's capability to do research on these agents. This will require that additional high containment research facilities (Biosafety Laboratory (BSL)-3 and BSL-4) will need to be constructed and accessible to government-supported scientists.

This program is designed to maximize the efforts of industry, academia, and federal researchers to accelerate the development of new and safer vaccines, therapeutic agents, and improved diagnostic tests. The NIH will facilitate this through the use of all available funding mechanisms with a focus on developing ten Extramural Centers of Research Excellence for Bioterrorism and Emerging Infections, expanding the availability of BSL-3/BSL-4 laboratories, expanding grants, contracts, and intramural research, and initiating challenge grants to industry and academia. The plan consists of four, broad interconnected efforts:

- Expand basic research on the physiology and genetics of potential bioterrorism agents, immune system function and response to each potential agent, and the pathogenesis of each disease.
- Accelerate discovery and development of the next generation vaccines, therapeutic agents, and diagnostic tests using knowledge from basic research.
- Expand clinical research on newly discovered and developed products to test for safety and effectiveness.
- Expand research infrastructure to enable biomedical research efforts on pathogenic microbes, including potential bioterrorism agents.

The NIH will convene a Blue Ribbon Panel on Bioterrorism-Related Research in February 2002 to obtain advice and input on the Bioterrorism-Related Research Agenda. The Panel will assess the current state of research related to bioterrorism, as outlined in the agenda, and make recommendations regarding priorities and implementation.

The NIH also has enhanced its security measures that are necessary for the protection of its staff and facilities. The agency closely monitors all activities in this arena, is alert to changes that are made at the Federal, State, and local level, and continues to ensure safety with a minimum of disruption to the NIH mission and operations.

Cancer

In spite of declining incidence rates overall, more than one million people are newly diagnosed with cancer in the U.S. each year. One of every two men and one of every three women develop cancer over the course of their lives. The incidence of some cancers – such as esophageal cancer, melanoma, and lung cancer in women – is still rising. Nearly 25 percent of

all deaths in our country are due to cancer. Cancer is the second leading cause of death in the U.S. – ranking behind only heart disease.

In FY 2003, the NIH will continue its comprehensive program of research and infrastructure activities to address the many unanswered questions about who gets cancer, at what stage of life, and why; provide researchers with the resources they need to conduct ongoing and new research; and support the kind of large-scale studies required to understand and better diagnose, treat, and prevent cancer. For example, supporting the creation of a resource of biological assays and chemical probes to allow investigators to identify and test cancer-related targets for drug discovery easily will enable a broad range of new cancer studies and will contribute significantly to our ability to develop new and better options for the prevention and treatment of cancer.

Support will also be provided for large-scale studies on critical cancer control, prevention, and screening questions. For example, the NIH will conduct the largest-ever prevention study to determine if vitamin E and selenium can protect against prostate cancer. The Selenium and Vitamin E Cancer Prevention Trial is the first study designed to look specifically at the effects of these two dietary supplements, both separately and together, in preventing prostate cancer. For this trial, NIH will be working in partnership with the Southwest Oncology Group, one of several cancer cooperative groups sponsored by the agency. The study will include a total of 32,400 men recruited through more than 400 sites in the United States, Puerto Rico, and Canada and is expected to take up to 12 years to complete. Prostate cancer is the second most common form of cancer in men, after skin cancer.

The NIH and another cooperative group, the American College of Radiology Imaging Network, will launch the first large, multicenter study to compare digital mammography to standard mammography for the detection of breast cancer. Digital mammography technology provides higher resolution images than standard mammography, and investigators want to determine if it can detect breast cancer more accurately. This Digital Mammographic Imaging Screening Trial will involve 49,500 women in the United States and Canada by comparing digital mammography to standard film mammography. Women will be entered into the study at the time of their regular screening mammogram. Each woman will then be followed for several years after receiving both digital and conventional mammograms. A total of 19 institutions in the United States and Canada will take part in the study.

Investigators who are part of an NIH Cohort Consortium will be working to uncover potential interactions of genetics and environmental exposure by combining data from prospective cohort studies involving 7,490 cases of breast cancer and 7,130 cases of prostate cancer. Interactions between established risk factors and a set of genetic variants associated with these cancers will be studied. This collaboration will provide the best source of data on these variants and the risk of these cancers, as well as maximizing statistical power and allowing rapid assessment of the consistency of findings across studies. The collaborative effort will serve as a model for future efforts that can take full advantage of investments in large population studies and increase our understanding of what is needed to better control, prevent, and treat cancer.

Asthma

Asthma is a chronic lung disease that affects an estimated 17 million Americans. When asthma strikes, airways in the lungs become inflamed and constricted, causing coughing, wheezing, and difficulty in breathing. Each year, nearly 500,000 Americans are hospitalized and more than 5,000 die from asthma. Children are more likely to develop asthma than adults, especially inner-city children. African Americans are hospitalized for asthma three to four times more often than other Americans, and African Americans are four to six times more likely than whites to die from asthma. Asthma appears to develop early in life, stemming from a combination of genetic and environmental causes. For unknown reasons, asthma is on the rise, increasing by 75 percent between 1980-1994, according to the latest available figures.

Efforts are needed to determine the causes of asthma and develop interventions to prevent its onset. Research has not yet identified or demonstrated how to prevent the onset of asthma. While research on various aspects of the origins of asthma is already underway, FY 2003 efforts will explore the potential for early life events that cause asthma, such as pre- and post-natal exposures to viral infections, allergens, tobacco smoke, and elements of the maternal and infant diet. Another high priority is the development of immunologic and clinical markers of asthma in infancy and early childhood among children of distinct genetic backgrounds. Efforts will include studies of gene-environment interactions and links to characteristics of asthma. Because allergens may play an important role in some adults with asthma who did not exhibit the disease in childhood, new efforts will focus on adult-onset asthma in stages of life such as during pregnancy, during menopause (especially in those on hormone replacement therapy), and in the elderly who have confounding medical complications. Intervention trials are also needed to test hypotheses of how to prevent asthma, even while work on understanding the basic mechanisms is proceeding. Tests of prevention strategies for those at high risk of developing asthma could include investigating whether eliminating various exposures during early life or providing pharmacologic treatments can delay or prevent the onset of the disease. Another promising strategy is to block the immune response to allergens in susceptible individuals, for example by induction of immune tolerance, thus preventing asthma from ever developing. Identifying interventions to prevent asthma is the most promising approach to ending the epidemic of asthma.

FY 2003 will also bring expanded efforts to promote wider use of current knowledge to diagnose and manage asthma. Currently, the NIH supports clinician education through the translation of research on asthma into clinical practice guidelines and practical health education materials and tools. The NIH sponsors a wide range of education and outreach activities to patients, clinicians, family members, school personnel, and caregivers through the National Asthma Education and Prevention Program.

In an effort to identify methods to reduce illness in those who have asthma, NIH currently devotes substantial resources to clinical trials evaluating and assessing treatment strategies, such as studies on the impact and safety of medications at different stages of children's development.

New efforts will seek to improve understanding of what makes asthma persistent and severe. Other efforts will be devoted to developing means of controlling triggers of asthma and the allergic response to them as well as to accelerate efforts to better understand the cellular and molecular mechanisms by which air pollutants perturb the normal functioning of cells, tissues, and organs. In addition to refining our understanding of the role of air pollutants in exacerbating asthma, this research will help determine whether they are implicated in the initial onset of the disease. FY 2003 efforts will include investigations of the variation in patient response to asthma medications. Not all patients respond favorably or in the same way to the same medications, and some patients experience adverse side effects from asthma medications. Patients would benefit from the development of both new treatments and the means for tailoring therapeutic approaches to the specific genetic and clinical characteristics of the individual's asthma. Efforts will be undertaken to establish causes and risk factors of asthma fatalities and develop non-invasive methods for diagnosis and disease monitoring. New technologies, such as imaging or biochemical markers of inflammation, and patterns of gene activation, will be employed to detect disease and monitor disease progression, particularly in these vulnerable populations.

Parkinson's Disease

Genetics, cell biology, and pharmacology are all contributing to new advances in Parkinson's disease upon which the NIH is building its growing effort to understand, prevent and treat this devastating disease. Genetic studies of Parkinson's disease are advancing on several fronts. New knowledge about less common inherited forms of the disease is leading to better understanding of the underlying processes that result in brain pathology. Several genes and their expressed proteins associated with Parkinson's disease have been identified, and efforts are now focused on understanding their role in the disease process.

Nerve cells that produce the neurotransmitter dopamine die in Parkinson's disease. Current treatment is based on replenishing the dwindling supplies of dopamine in the brain. However, this treatment does not slow the underlying death of nerve cells and ultimately fails as the disease progresses. To address this underlying problem, efforts are now underway to expand the work at more than 40 clinical centers to test neuroprotectants – drugs that actually slow or stop the progression of the disease. Replacing these cells may, however, be the best hope for people with advanced disease. This year the first controlled clinical trial to test fetal tissue transplantation showed that the problems outweighed the benefits for the particular procedure used. However, the trial provided proof in principle for cell therapy – transplanted cells survived, produced dopamine, and altered movement control. Experiments in rodent models of Parkinson's suggest that stem cells may ultimately provide better methods for cell replacement therapy, and NIH is funding primate studies as a step toward human trials.

Many of these efforts and the ones planned for FY 2003 emerged at a January 2000 workshop, at which intramural, extramural, and industry scientists, representatives from several Parkinson's disease advocacy groups, and ethicists held intensive discussions which formed the basis of the "NIH Parkinson's Disease Research Agenda." The Agenda encompasses research from basic

studies to understand the normal brain functions disrupted by this disease through clinical studies of therapeutic strategies, including drugs, cell replacement, gene manipulations, and surgery.

NIH is aggressively undertaking various activities to carry out this Research Agenda. Grant solicitations include: the role of the environment in Parkinson's disease and career development awards in the role of the environment in Parkinson's disease; consortium on deep brain stimulation for the treatment of Parkinson's disease; function of synaptic proteins in synaptic loss and neurodegeneration; role of parkin and related proteins in Parkinson's disease; mitochondrial function in neurodegeneration; and mechanisms of action of deep brain stimulation, among others. The NIH is also implementing fast track grants for Parkinson's disease research and supplementing programs to expand ongoing grants to include research to screen FDA-approved compounds for use against neurodegenerative diseases and on DNA microarray analysis. Supplements to center grants will also be made to carry out additional research on high-throughput screening to find candidate compounds for Parkinson's disease drugs, sharing of biological reagents relevant to Parkinson's disease, and Parkinson's disease brain banking.

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive, currently irreversible brain disorder. People with AD gradually suffer memory loss and a decline in thinking abilities, as well as major personality changes. These losses in cognitive function are accompanied by pathologic changes in the brain which result in death of brain cells and breakdown of the connections between them. AD is a major public health issue for the United States because of its enormous impact on individuals, families, the health care system, and society as a whole. As the U.S. population ages, the number of people with AD and the costs associated with increased prevalence could rise significantly.

Early diagnosis of AD benefits everyone involved, from affected individuals and their families to clinicians and researchers. For patients and their families, a definitive diagnosis early in the course of the disease provides an opportunity to plan and pursue options for treatment and care while the patient can still take an active role in decision-making. For clinicians, accurate early diagnosis facilitates the selection of appropriate treatments, particularly as new interventions are developed to stop or slow progression of symptoms.

Research findings at the molecular level have created new and unprecedented opportunities for translation of basic research into clinical applications. Newly created animal models of AD permit rapid testing of potential treatments based on new genetic and molecular targets. The process is necessarily deliberate; as new target molecules are identified, plans are in place to test new interventions in animal models for safety and efficacy.

Basic research also suggests that the earliest AD pathology may begin to develop in the brain 10 to 20 years before clinical symptoms yield a diagnosis. Recent discoveries have identified the genetic and cellular pathways that mediate AD, including plaque and tangle formation and death

of brain cell. Until 2001, just four of the approximately 30,000 genes in the human genome were conclusively known to affect the development of AD pathology. Three of these genes are associated with early onset AD, and only one is associated with the more common form of the disease, late-onset AD. Recent genetic studies suggest that as many as four additional and as yet unidentified genes may also be risk factors for late-onset AD. To facilitate the identification of AD risk factor genes, NIH is planning an expansion of its National Cell Repository. A national resource for research on AD, the Repository was created to collect DNA, cells, and information from families with multiple affected individuals with AD. Its activities include the production of a catalog of cell lines and DNA samples that are available for qualified scientists to study.

Trials are also needed for interventions that prevent AD onset or progression. In FY 2003, new prevention efforts will focus on candidate agents, including anti-inflammatory agents, anti-oxidants, estrogen, and statins among others. Testing of new methods for early diagnosis of AD, based on imaging and markers of early brain changes is also needed. Scientists are developing and refining powerful imaging techniques that target anatomical, molecular, and functional processes in the brain. These new techniques hold promise of earlier and more accurate diagnosis of AD, as well as improved identification of people who are at risk of developing the disease.

Diabetes

Diabetes is estimated to affect close to 16 million people in the U.S. Diabetes is not one disease – rather, it is a group of diseases characterized by high levels of blood glucose resulting from defects in insulin secretion, insulin action, or both. Diabetes is a chronic disease and can result in serious complications and premature death if not well-managed by patient and caregiver. There are four types of diabetes: Type 1 diabetes (insulin-dependent diabetes or juvenile-onset diabetes); Type 2 diabetes (non-insulin-dependent diabetes mellitus or adult-onset diabetes); gestational diabetes; and “Other specific types” of diabetes that result from specific genetic syndromes, surgery, drugs, infections, and other illnesses.

Recent data show that over the past decade and even over the past year, there has been a dramatic increase in obesity and type 2 diabetes in the U.S. across all age groups, including adolescents, and in all racial/ethnic groups, with Hispanic-American, African-American, and Native American groups particularly severely affected. If this trend continues unabated, the already enormous human burden and health care costs of diabetes are projected to grow to levels that could threaten the U.S. health care system. Fortunately, the recently completed Diabetes Prevention Program trial provided proof of principle that modest lifestyle changes can prevent type 2 diabetes in high-risk people with impaired glucose tolerance. The impetus now is to develop more effective methods to identify individuals with impaired glucose tolerance and to intervene. Cost effective approaches directed at providers, high-risk individuals, and communities to support achieving these lifestyle changes must be developed and validated. Research is needed to: 1) understand health care providers' knowledge, attitudes, and skills related to diabetes prevention and how providers can be encouraged and enabled to provide

effective lifestyle intervention; 2) understand an individual's knowledge about personal risk and the importance of prevention and how they can be motivated and empowered to achieve lifestyle change; and 3) understand and alter social, environmental, and community factors that influence lifestyle and choices. A trans-NIH Request for Applications focused on research addressing these issues is under development for FY 2003.

With respect to type 1 diabetes, NIH scientists are continuing research on islet transplantation in humans, and preliminary studies appear promising. Other research will include, for example, an oral insulin study of the Diabetes Prevention Trial for Type 1 Diabetes, for which recruitment has begun. Investigators have also convened meetings to plan clinical studies on type 1 diabetes as part of the Diabetes TrialNet. The TrialNet will include clinical centers, recruitment networks, and a coordinating center. It will provide the research infrastructure needed to foster the future design and execution of pilot studies and expanded clinical research. The TrialNet will permit more rapid clinical testing of novel approaches to treatment and prevention. The NIH plans to investigate ways in which interventions that have already been demonstrated to be beneficial by laboratory or clinical investigations can be extended or adapted to larger populations to improve health care delivery and diabetes self-management and to promote healthy lifestyles to reduce the risk of diabetes and obesity. To continue to build fundamental knowledge that could eventually lead to novel ideas for diabetes care, the NIH will develop a Beta Cell Biology Consortium to focus on research on beta cell and pancreas development; this will also include the study of human embryonic stem cells in accordance with criteria established by the President. The NIH will also support studies on an important group of proteins called orphan receptors. To advance research on diabetes and related areas of endocrinology and metabolism, the NIH will strive to expand diabetes research centers to bring together clinical and basic science investigators from relevant disciplines.

Minority Health and Health Disparities

Efforts to address disparities in health among minorities and other disadvantaged populations compared to the majority, remain a top priority of the NIH. This research emphasis is also consonant with the priorities of Congress and the Administration as reflected in passage of Public Law 106-525 which created the National Center for Minority Health and Health Disparities (NCMHD) and by the establishment of the NCMHD by the Secretary of Health and Human Services on January 16, 2001.

There are complex factors that underlie disparities in health status – factors that converge and cause differences in disease progression and in health outcomes. While the diversity of the American population is one of the Nation's greatest assets, one of its greatest challenges is reducing the profound disparity in health status of America's racial and ethnic minorities and rural populations, including Appalachian residents, and other similar groups, compared to the population as a whole. And, although some of the causes of disparate health outcomes, such as differences in access to and reimbursement for care, are beyond the scope of much biomedical

and behavioral research, the NIH plays a vital role in addressing and easing health disparities involving cancer, diabetes, infant mortality, AIDS, cardiovascular illnesses, and many other diseases.

Infrastructure support is an essential part of the framework for the conduct of high quality research and a means of facilitating the participation of minority institutions in such research. For example, the Centers of Excellence Endowment Program will provide enduring and forward-looking support for the minority health and health disparities research programs at emerging institutions of excellence. NIH will continue to provide support for the Institutional Development Award (IDeA) Program, which fosters health-related research and increases the number and competitiveness of investigators in institutions located in States which, historically, have not fully participated in receiving NIH grant awards. The NIH also makes awards for the Biomedical Research Infrastructure Networks (BRIN), the purpose of which is to promote the development, coordination, and sharing of research resources and expertise throughout the state for planning over several years to enhance the research infrastructure and increase the number of competitive investigators. The Resource Centers for Minority Aging Research are enhancing professional diversity in minority health research, evaluating/developing measurement tools tailored to minority populations, and developing strategies for recruiting and retaining minority research participants.

Plans are also underway to develop Partnership Programs of Excellence in Minority Cardiovascular Health Research. Important aspects of the programs will include community involvement in the research, outreach strategies for patient recruitment and retention, and development of new investigators interested in reducing cardiovascular health disparities. The NIH will also continue research-based health education activities on diabetic retinopathy in the Mexican-American population who are known to have a high rate of diabetes along with more severe hyperglycemia, which indicates poor glucose control. Other efforts include research on drug abuse and addiction, including efforts to reduce the impact of HIV/AIDS and other disease consequences of drug abuse in minority populations; identifying underlying mechanisms of gender and ethnic differences in the etiology of alcoholism and alcohol-related tissue damage, which is a prerequisite for developing effective treatments for alcoholism and alcohol-induced organ damage in women and ethnic minorities; research to prevent or reduce oral health disparities; an expanded program of Specialized Neuroscience Research Programs; projects involving African Americans affected with diabetes and hereditary prostate cancer; and research on HIV treatment and prevention research, hepatitis C virus, asthma, and autoimmunity – conditions that disproportionately affect minority communities. The NIH and its national, State, and local partners will be working to better understand and address the high cervical cancer mortality rate that exists in much of rural America. Despite a three-fold reduction in cervical mortality nationwide in the past 50 years, counties stretching from Maine southwest through Appalachia to the Texas/Mexico border as well as in many Southeastern states and in the Central Valley of California have experienced persistently higher cervical cancer mortality rates. The effort includes synthesizing existing research knowledge; identifying core findings; articulating program and policy options; and disseminating this information to Federal, State, and local officials to inform policy and programmatic decisions.

SCIENCE ADVANCES

The following section provides examples of some of NIH's most significant achievements in FY 2001. They are the outcome of many and varied investments in medical research by the NIH, some of which began more than a decade ago.

New Understanding of Complex Biological Systems

New knowledge about complex biological systems in both animals and humans is essential to the development of tomorrow's diagnostic tools, prevention strategies, and treatments.

New Treatment for Leukemia. NIH researchers have developed a new treatment for hairy cell leukemia, a rare, slow-growing cancer of white blood cells, which represents about two percent of all leukemias. About 20 percent of patients who have high levels of hairy cells circulating in their blood respond poorly to current treatment. The new treatment uses a specially designed molecule to deliver a deadly toxin directly to the leukemia cells. Designed to reach a tumor target quickly and directly, the new molecule acts by binding to a cancer cell, delivering its poison, and killing the cell. Its specificity for cancer cells keeps it from harming healthy cells, a common and clinically significant consequence of more traditional cancer therapies. Of the 16 patients who participated in this trial, 11 experienced complete remission and another two partial remissions. If confirmed in further trials, these results offer new hope for patients suffering from hairy cell and other types of leukemia.

Early Signs of Alcohol Abuse. Researchers have discovered a striking association between the age of first alcohol use and development of alcoholism later on in life. A recent study showed a high correlation between early age drinking and a number of signs of neurological and behavioral disorders, such as attention-deficit disorder and impulsiveness. In addition, adolescents who began drinking at a young age were shown to be more likely than others to have a brainwave abnormality that has been shown in previous studies to indicate increased risk of developing alcoholism. This finding suggests that early drinking may be, at least in part, physically based.

A New Animal Model for Parkinson's Disease. Parkinson's disease is a progressive neurodegenerative disorder characterized by selective death of neurons that make dopamine, a neurotransmitter in a specific region of the brain. Although there may be a genetic component to Parkinson's disease, environmental influences, such as pesticide exposure, may also play an important role in its origin. Recently, scientists developed a model of the disease using rats exposed to a common pesticide called rotenone. Rotenone-treated rats displayed motor behavior abnormalities, such as rigidity and decreased motor activity, which are frequently seen in Parkinson's disease patients. Rotenone inhibited the activity of an enzyme responsible for energy metabolism throughout the body, including the brain. It also caused a selective degeneration of dopamine neurons in the substantia nigra of the brain. This new model of

Parkinson's disease will be useful in designing and testing new therapeutic interventions, as well as further identifying environmental exposures that may be risk factors for developing the disease.

Potential Vaccine for Ear Infection in Infants. Today, at an estimated cost of approximately five billion dollars per year in the U.S., an ear infection is the most common reason for childhood doctor visits. Recently, NIH scientists have developed candidate vaccines that would protect infants from an ear infection caused by two major bacterial pathogens: nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis*. In an early clinical trial involving 40 normal human adult volunteers, one such vaccine directed against *H. influenzae* proved to be both safe and effective. This candidate vaccine will soon be tested in a second trial for safety and effectiveness in children. Several vaccine candidates have been identified for *Moraxella catarrhalis* and clinical trials are also planned to test these candidate vaccines for safety and efficacy in humans. These studies are significant advances towards the long-term goal of developing a multivalent vaccine that reduces the incidence of childhood ear infection caused by all major bacterial pathogens.

Understanding Mad Cow and Related Diseases. Prions are harmful proteins found in devastating neurological diseases such as Creutzfeldt-Jakob disease (CJD) in humans and bovine spongiform encephalopathy (mad cow disease) in animals. Although the incubation time for CJD may be decades, once symptoms appear the destruction of the brain progresses rapidly, typically to death within one year. CJD presents a scientific puzzle because the disease can be spontaneous, inherited, or transmissible, and the agent responsible is not a conventional virus or bacterium. Recently, scientists have discovered an unlikely model for prion diseases – baker's yeast. The yeast provides insights not only into prion formation, but also into amyloids, which are abnormal forms of protein observed in neurological diseases such as Alzheimer's disease. Yeast has its own set of prions, which, like those of animals and people, often start out as normal proteins, but then spontaneously change into a sinister form. One such yeast prion is called URE3, which is an altered form of a normal yeast protein called Ure2p. Scientists recently learned that these prions use other proteins as unwitting accomplices to help them convert normal proteins into prions. URE3 prions have also been shown to aggregate and form amyloid filaments, which resemble amyloid found in a number of human diseases, including Alzheimer's, late-onset diabetes, multiple myeloma, and transmissible spongiform encephalopathies. Continued research on yeast prions will generate further insights into both prion disease and amyloid formation.

A New Agent to Prevent Organ Transplant Rejection. Researchers have discovered a new agent (anti-CD154 antibody) that prevents organ rejection, but does not have the toxic side effects associated with conventional therapies. Scientists recently designed a study to determine the most efficacious treatment regimen of this new agent in a model of kidney transplant (monkeys). Following a course of anti-CD154 therapy as short as one month, scientists found that the animals experienced marked rejection-free organ survival for a limited period of time.

Although its effects did not last indefinitely, anti-CD154 antibody is a promising agent with extraordinary efficacy.

Improving Treatment for Breast Cancer. One of the most significant breakthroughs in breast cancer treatment is the chemotherapy agent, taxol. It is a highly toxic drug, but it is this very toxicity that enables it to kill breast cancer cells that have spread in the body. Women vary greatly in their tolerance of this drug and finding the correct dosage is one of the many challenges facing women when they undergo chemotherapy. Presently, the established procedure is to start with a “standard” dose and then determine the dosage appropriateness from a woman’s reaction to the drug. Improved ways to individualize the dose would be of obvious benefit to women during this difficult time. Like many drugs, taxol circulates in the body until it is broken down or metabolized by enzymes and then subsequently excreted. Genes coding for these enzymes can have subtle variations, or polymorphisms, that can render the enzyme more, or less, capable of metabolizing drugs or foreign agents. If the polymorphism results in an enzyme with less activity, then the drug circulates much longer in the body than it would in normal people. Thus, what would be considered a safe dose in one patient would be too high in people with a less active metabolizing enzyme. Recently, NIH-supported scientists discovered a polymorphism in humans which dramatically decreased the metabolism of taxol. Genetic tests have been devised to assay for this polymorphism in human blood cells and to determine if there is an association between this polymorphism and the therapeutic efficacy and/or toxicity of taxol. If clinical studies bear out these findings, oncologists will have a valuable tool in determining the correct and tolerable doses of taxol to administer to their patients.

Harmful Brain Changes in Alzheimer’s Disease. Many scientists suspect the root cause of Alzheimer’s disease (AD) is formation of plaques, which result from the excessive production of an amyloid protein (APP) produced by a mutant gene. Another key feature of this disease’s pathology is the neurofibrillary tangle made of insoluble aggregates of the *tau* protein, which causes cell death. For the first time, researchers produced a mouse model for AD that includes both mutant genes APP and tau (double transgenic mice). This is the first animal model in which the elusive connection between amyloid pathology and tangle formation can be investigated. This improved animal model for AD may also be critical for success in developing therapies against tangle formation and the death of brain cells.

Finding Genes Responsible for Autism. Autism is a neuropsychiatric disorder that clinically manifests itself as a social disorder characterized by lack of social interaction, severe language impairment, restlessness, distraction, and stereotyped motor behaviors. Approximately 1 in 2,000 – 2,500 children is born with autism, affecting boys to a much greater extent than girls by a ratio of 3:1. In order to understand the root cause of autism, the location(s) of autism-related genes need to be identified. Researchers have carried out an extensive genome-wide screen for autism, involving 110 families, and analyzed 335 markers (or DNA regions). Each family included in the study had at least two affected members, at least one of whom was diagnosed with autism and the other with a pervasive developmental disorder or Asperger’s syndrome. Statistical analysis of different DNA regions suggested three likely locations on the

chromosomes that are associated with autism. The strongest statistical linkage was located on the long arm of the X chromosome. The next two strongest linkages were located on chromosomes 5 and 19, respectively. Linkages to similar chromosomal regions on X and 19 had been previously found by other researchers, lending support to the new findings that genes important in the development of autism may be found in these areas.

How Anthrax Destroys Cells. Many years of research on anthrax fortuitously are offering promise just as the disease became the focus of a biological terrorism attack gripping the United States. The anthrax bacterium causes illness and death by releasing toxins that kill cells and damage organs. NIH-supported scientists have pinpointed the protein receptor, the area on the surface of human cells, to which anthrax attaches in order to gain entry into the cell. Researchers demonstrated in the laboratory that a synthetic version of the anthrax toxin receptor, containing the toxin-binding segment, blocks the entry of the toxin into cells and protects the cells from destruction. Without the synthetic receptor, a part of the toxin attaches to the human cell surface receptor, creates a hole in the human cell membrane, and injects another part of the toxin called "lethal factor," which destroys proteins in the cell. Another group of NIH-supported scientists has deduced the structure of this "lethal factor." Thus, researchers have identified how different parts of the toxin exert their effects, and have shown how at least one molecule can completely protect cells from destruction. These discoveries offer promising new ways to treat anthrax, including drugs that either keep the toxin from entering cells or that block its ability to disrupt the cells' function.

Develop New or Improved Methods for Diagnosing Disease and Disability

Research to create new diagnostic tools is closely intertwined with basic disease research. Once the mechanisms of the specific disease process are understood, it then becomes

possible to develop new or improved diagnostic tools.

Detection of Colorectal Cancers Without Colonoscopy. Colorectal cancer accounts for the second largest number of cancer deaths in the U.S. Its early detection improves survival, but the current detection methods involve testing for occult, or unseen, blood in the stool, or the much more invasive colonoscopy. Scientists observed that colorectal cancer cells are shed into the stool, and their goal was to develop reliable, specific molecular genetic tests for cancer detection from stool samples. Colorectal cancer often has a fairly small number of genetic alterations: 1) mutations that activate a cancer-causing gene called *K-RAS*, 2) mutations that inactivate the tumor suppressor genes *APC* and *TP53*, and 3) some mutations of the genes that repair mismatched DNA. Finding, isolating, and analyzing the tiny amount of tumor DNA posed daunting technical problems, but by using three different assays for K-RAS, TP53, and BAT26 genetic material, scientists isolated and accurately identified the cancers of about three quarters of the patients they tested. The researchers now plan to look at ways to improve K-RAS availability and to look at genes that were not included in this analysis. If they can include detection of the APC tumor suppressor gene using such techniques, theoretically, 90 percent of

colon cancers could be detected early using such non-invasive methods. In addition to potentially improving early detection of colorectal cancer, these laboratory techniques may be useful for tests to assess other fluids such as sputum in lung cancer patients, urine in bladder and kidney cancer patients, seminal fluid in prostate cancer patients, and mammary duct effluents in breast cancer patients.

A New and High-resolution Microscope for Viewing Living Cells. The best microscopes available to scientists today allow them to examine the molecular details of cells, but in order to do so, the cells must be treated with resins or dyes, which either kill the cells or fundamentally alter their behavior. Magnetic resonance imaging, on the other hand, allows physicians to view the real-time, unaltered functioning of the body, but its resolution is not fine enough to provide a view of individual cells. To capture the best of both instruments, a multidisciplinary team of NIH-funded physicists, biologists, optical experts, and chemists developed a new type of microscope combining the capabilities of nuclear magnetic resonance imaging with those of a traditional microscope. Using the combined microscope, investigators will now be able to examine how living cells react to changes in their environment, track the development of cancer, and study how cancer cells respond to treatment.

Blood Test Can Predict Pulmonary Complications from Sickle Cell Disease. A pneumonia-like illness known as acute chest syndrome (ACS) is the leading cause of morbidity and early death in patients with sickle cell disease. Although ACS often develops in the course of sickle cell crises, it has not been possible to predict whether a given patient would develop ACS. However, researchers studying patients who were hospitalized for sickle cell crises found that elevated levels of an enzyme called secretory phospholipase A₂ are associated with development of ACS. Although the classic symptoms of ACS appear with little warning, the levels of this enzyme in the blood increased 24 to 48 hours before ACS could be diagnosed clinically. If these results are confirmed by larger clinical studies, enzyme measurements could be used to identify patients with impending ACS. Early diagnosis will allow treatment to be initiated before severe ACS develops, thereby reducing the morbidity, mortality, and costs associated with this complication.

Computer Distinguishes Different Tumor Types. For many cancers, early and accurate diagnosis can improve outcome. Scientists have recently developed a method of genetic fingerprinting that can distinguish a group of childhood cancers which have a similar appearance under a microscope and are difficult to differentially diagnose. For these childhood cancers, such diagnoses are often imprecise and few children survive. The method combines, for the first time, the cutting edge DNA sequencing technology (microarray) with a form of artificial intelligence (a computer mimicking human thinking) called an artificial neural network. The neural network automatically analyzes the enormous amounts of data produced by the microarray resulting in a highly accurate diagnosis. The research team started by surveying the expression of over 6,000 genes. The neural network analysis narrowed that number down to a mere 93 unique genes needed to differentiate the four tumor types. And of those, 41 were new genes that might provide

important insights into the biology of these cancers. This technology is also accelerating research to cataloging and characterization of the genes involved in cancer development and progression.

Understanding Gene Functions – Mouse Gene Database. Genes are crucial for understanding biological processes in early development and aging. A collection of 15,000 mouse genes has been developed, with emphasis on inclusion of genes active in placenta and embryo development. Nearly complete sequences of each gene in the 15K gene set are available. By comparing the sequence information with genes that have already been well studied, scientists may be able to determine the function of these genes in mice. So far, 4,027 genes have been assigned to biologically important functions, including apoptosis (cell death), cell cycle, matrix/structural proteins, energy/metabolism, transcription/chromatin, protein synthesis/translational control, signal transduction, heat shock stress protein, and DNA replication. To facilitate extensive use of this gene collection in aging and other life science research, the set is being made freely available as a resource to the scientific community. To date, this collection has been distributed to more than 100 research institutions world-wide.

Interpreting Tumor Data. The ability to monitor tumor progression is crucial to controlling and preventing the many different forms of cancer. A vast amount of data about tumors is being produced by cutting edge DNA sequencing technology. Critical to data interpretation is the development of new and improved computer software models and programs. NIH-supported scientists have developed a “tree” model to analyze tumor DNA data. This mathematical model is being used to analyze chromosomal mutations in tumors and is allowing researchers to begin to predict genes responsible for tumor initiation and progression – the first steps towards diagnosis, prevention, treatment, and even cure.

Bladder Cancer Diagnosed by a Simple Urine Test. There is currently no simple, approved test for bladder cancer. Scientists recently developed a urine test for this purpose which involves a protein called “survivin.” The rationale for developing a screen for the presence of survivin was based on two pieces of information: 1) that this protein inhibits cell death that normally occurs as new cells are formed; 2) that abnormal survival of mutated cells may lead to cancer; and 3) that survivin is made by cancer cells and released into urine, but it is not made by most normal cells. Thus, scientists developed a screen for survivin in urine as a sign of cancer. The test proved very sensitive, detecting survivin in all of the bladder cancer patients studied. It also gave very few false-positives and was simple and cost-effective. With this advance, a non-invasive urine test for bladder cancer may become routine.

Visible Images of Strokes. Diffusion Tensor Magnetic Resonance Imaging, or DT-MRI, is a form of magnetic resonance imaging (MRI) that provides more detailed anatomical information about tissue structure, composition, architecture, and organization in a living human being than conventional MRI. Scientists who invented DT-MRI have produced detailed maps of the human brain and are applying this new technology to assess and diagnose neurological and developmental disorders. The recent innovation allows scientists to examine the permanent degeneration of nerve tissue, often associated with chronic stroke, by identifying and

differentiating pathways that suffer from a lack of blood supply during the event. Moreover, DT-MRI is allowing scientists to perform detailed studies of the brain's structure, which previously could only be examined using labor-intensive and invasive methods. By using DT-MRI to visualize neurological pathways, scientists have, for the first time, begun to be able to examine a stroke in progress. Researchers testing new medication to prevent or treat brain damage that results from stroke will be able to use DT-MRI to evaluate the treatment. This new ability to study the brain's pathways non-invasively will likely prove valuable in diagnosing and possibly treating a range of neurological diseases.

Nursing Care Improves Survival Rate of Sudden Cardiac Arrest. Sudden cardiac arrest remains one of the leading causes of death in the U.S. Improving the short-term survival rate of patients who have suffered sudden cardiac arrest is crucial to the long-term recovery. NIH-funded researchers have shown that nursing care could improve the two-year survival rate of survivors of sudden cardiac arrest by 86 percent. This nursing intervention consisted of three components: a physiologic relaxation training using biofeedback; a cognitive therapy aimed at self-management and coping for depression, anxiety, and anger; and health education focusing on cardiovascular risk factors. Eleven sessions were held twice a week over a four- to six-week period. This study serves as a control for other clinical predictors of death, including different pharmacologic therapies. Although the specific mechanism for these positive results is not known, this research provides strong support for the use of psychosocial treatment of survivors of cardiac arrest.

Detection of Prenatal Cocaine Exposure in Newborns. Illegal drug use by pregnant women remains a difficult problem in the area of substance abuse in the U.S. Each year, approximately 5.5 percent of pregnant women report using an illicit drug at least once during their pregnancy. Accurate determination of prevalence of drug use is the key to early interventions. Researchers have found that they can better estimate prenatal drug exposure by analyzing meconium (stool) specimens of newborns with gas chromatography/mass spectrometry (GC-MS), followed by a maternal hospital interview. GC-MS is a sensitive instrument which accurately "fingerprints" specific organic compounds within a small biological sample. This large-scale meconium analysis, co-sponsored by NIH and several other agencies, was part of the four-site Maternal Lifestyle Study (Detroit, Miami, Memphis, Providence) over a two-year period. This study involved 11,811 mothers, and over 8,500 meconium specimens were collected and analyzed for metabolites of illicit drugs such as cocaine, opiates, cannabinoids, PCP, and amphetamines. Prevalence and observed metabolites showed considerable variation across the four sites, and exposure status was higher in low birth weight infants. Based on the combination of meconium analysis and maternal self-report, 10.7 percent of the infants had cocaine/opiate exposure, with the majority (9.5 percent) exposed to cocaine. There was 66 percent agreement between positive meconium results and positive maternal report. Only 2 percent of mothers reported that they used only cocaine during pregnancy and mothers who used cocaine were 49 times more likely to use another drug. Thus, meconium testing provides an excellent tool for helping determine these numbers. By using meconium testing and self-report data, children prenatally exposed to drugs can be identified more easily and appropriate medical care, early psychosocial interventions, and

special education services can be offered. This study also confirms previous studies which suggest that cocaine is not used alone, it is typically used with other drugs; thus prenatal exposure is likely to be a multiple-drug problem.

Tracking the Behavior of Malaria-carrying Mosquitoes. Malaria is a mosquito-borne infection that causes close to 3 million deaths annually, primarily among children under the age of five living in sub-Saharan Africa. To better control and prevent the spread of malaria, it is critical to understand the behavior of the mosquitoes transmitting the disease; their feeding patterns vary widely by species and geographic location. An important research focus has been the source of food for the development of mosquito larvae. NIH-supported investigators from the United States and their counterparts in Africa have identified maize pollen as a food source for larvae-stage mosquitoes. They also established a strong correlation between the distribution of maize pollen in the vicinity, as well as the physical appearance of the water where mosquitoes breed, and the intensity of malaria transmission. These discoveries offer some new approaches toward preventing malaria transmission. For example, although eliminating maize is not practical in Africa because of its importance as a food crop, genetic modification of maize plants to alter pollen production may provide a potent anti-malarial intervention.

Nutritional Supplement Shows Promise for Treating Huntington's Disease. Huntington's disease (HD) results in progressive neural degeneration over a period of years beginning at mid life and ultimately, leading to death. To date, an effective treatment for HD remains elusive. In addition to genetic approaches, researchers are looking for other alternative treatments. Recently, researchers have tested the nutritional supplement creatine in a mouse model and observed improvement in survival, body weight, and motor function. These findings suggest that the progress of HD is linked in part to the failure of the body to manufacture creatine; directly supplementing creatine may be a new strategy to slow the disease process.

More Innovative Ways to Deliver Drugs to Specific Targets. There are many advantages to delivering drugs to a specific location in the body. It would allow for lower drug dosages, more effective therapies tailored to a specific disease, and fewer side effects. However, the potential of designer-delivery systems has not yet been realized. With support from NIH, scientists are exploring two new methods for drug delivery. The first method involves delivery of a drug via the lung by suspending a specific drug (protein) in ethanol. This method allows a reproducible dosage of drug without loss of biological activity of the drug or toxic effect of the suspending agent on the tissue. The second method involves condensing the drug into small structures made up of polymers (repeating chains of organic compounds) called nanostructures. Like the first method, this delivery system is not toxic and the drug also retains its biological activity. These new drug delivery methods have opened new opportunities for administration of many therapeutic agents. Potentially, they could have a wide range of clinical applications that lead to more efficient and less toxic drug treatment in the future.

New Approaches to Treatment: Gene and Cell Therapy

Gene or cell replacement continues to be a promising approach to treating complex genetic disorders.

Researchers have developed methods to isolate and purify donor cells and deliver them to the diseased

sites. In many cases, successes have been observed in animal model studies, where therapy led to tissue regeneration and restored functions.

Isolation of Pure Skin Stem Cells: Potential Treatment for Skin Diseases. The difficulty in isolating a pure epidermal (skin) stem cell population from adult tissues has been a barrier to its use in gene therapy or bioengineering techniques for the treatment of skin diseases. NIH-funded researchers have developed a novel cell sorting method that separates stem cells from other types of epidermal cells. The sorting method yields three categories of mouse epidermal basal cells: stem cells, transient amplifying cells, and non-proliferative basal cells. The stem cells proliferate for a lifetime, while the transient amplifying cells, already committed to becoming skin cells, will divide a finite number of times before they are sloughed off. The non-proliferating basal cells exhibit characteristics of proliferating cells, but do not divide. Scientists were able to validate the identity of the stem cells by their known characteristics: high proliferative capability, ability to regenerate tissue, and long-term gene expression, or activity. This novel sorting method yields pure, viable epidermal stem cells that might be useful for bioengineering skin tissue.

Additionally, the evidence of long-term gene expression means that these cells could be used in gene therapy for correcting skin diseases. This technology also may be useful for isolating stem cells from other epithelial tissues.

The Therapeutic Promise of Adult Stem Cells. Stem cells are undifferentiated cells that have the ability to make copies of themselves and also differentiate (take on the specialized function of an organ or tissue). Previously, it was believed that stem cells derived from adults could only differentiate into a limited range of tissues. Now, scientists have shown that a single, pure blood stem cell (hematopoietic) from male mice, when transplanted into the bone marrow of female mice (whose bone marrow cells were completely destroyed), could generate not only all of the different types of blood cells, but also cells in other parts of the body, including the liver, skin, lungs, and digestive system. In another example, researchers have shown that stem cells derived from bone marrow could generate new heart muscle in mice after induced heart attacks. They showed that the injected cells migrated to the damaged area and generated new heart muscle and blood vessels. This offers hope that damage due to heart attacks in humans can be repaired with cells from the patients' own bone marrow, thus avoiding the rejection problems associated with transplants using external donor sources. These studies demonstrated that adult stem cells have greater "plasticity" and motility than was previously believed. If they behave in humans as they do in mice, adult stem cells may have tremendous therapeutic potential. Stem cells derived from a patient's own body might someday be used to repair a damaged organ. Furthermore, the ability of stem cells to migrate to different areas of the body may be used to deliver drugs or gene therapy directly to sites needing repair.

Curing Retinal Degeneration in Inherited Eye Diseases. In some inherited eye diseases (like retinal degeneration), only one of the pair of corresponding genes normally found on a chromosome (one gene on each strand of DNA) needs to be mutated to cause the disease. These are called dominantly-inherited diseases. One approach to curing these diseases is to turn off the mutated gene, while leaving the normal gene intact and functional. Researchers have successfully applied this approach to cure retinal degeneration effectively in animal models for up to eight months. They were able to deliver ribozymes – small RNA molecules – to the cells adjacent to the retina of the eye. The inserted ribozymes acted like scissors and cut the messenger RNA produced by the mutated gene. This disruption turned off the mutated gene, while leaving the healthy one alone. This treatment approach holds promise for other diseases, where only one gene of the gene pair contains the mutated form responsible for the disease.

For more than a century, the NIH has guided the Nation and the world to new treatments and new strategies to prevent disease and disability. Nowhere is this more evident than its role in the deciphering of the human genome, arguably one of the most important landmarks in modern biology. At the dawn of the 21st century, the challenge for the NIH is to translate and convert information from this ‘book of life’ into effective prevention and treatment of diseases for all Americans and for the citizens of the world.

Unlike a century ago, efforts to meet the challenge to find new and more effective ways to probe complex living systems will require close collaborations between and among scientists from an even wider range of disciplines, including chemistry, biology, genetics, mathematics, computer science, engineering, and physics – efforts on a previously unimagined scale. The current era will require talented scientists who have the training, the instruments, and the facilities to conduct this important research.

The American people continue to place both great trust in and great responsibilities on the NIH. As before, the nation’s investment in the NIH, represented in the FY 2003 budget, promises to yield tangible returns in both the length and quality of life for ourselves, our families, and the generations that come after us. It is an investment in which we can all be proud.

FY 2003 BUDGET POLICY

The Fiscal Year 2003 President’s budget requests \$27,335 million for NIH, an increase of \$3,902 million, or 16.7% over the FY 2002 estimate, and an increase of \$3,712 million or 15.8 percent when including the FY 2002 Emergency Response Fund. The budget completes the President’s commitment to double the FY 1998 appropriation level in five years. Of this amount, \$76 million is requested from the Veteran’s Administration/Housing and Urban Development Appropriations Subcommittee for Superfund research activities. The NIH President’s budget

request to the Labor/Health and Human Services/Education Appropriations Committee is \$27,259 million.

This budget request for FY 2003 includes \$91.1 million for accrued retirement and health benefits associated with the proposed Managerial Flexibility Act of 2001. This legislation requires agencies, beginning in FY 2003, to pay the full Government share of the accruing cost of retirement for current CSRS, CIA and Foreign Service employees, and the Coast Guard, Public Health Service and NOAA Commissioned Corps. The legislation also requires agencies to pay full accruing costs of post-retirement health benefits for current civilian employees. The intention of the legislation is to budget and present the full costs of Federal employees in the accounts and programs where they are employed. This legislation is part of an initiative to link budget and management decisions to performance by showing the full cost of each year's program operations together with the output produced that year. These accrual costs are shown comparably in FY 2001 and FY 2002. Within the FY 2003 budget request, NIH will devote \$2.775 million for the payment of accrued costs for Commissioned Corps personnel.

The FY 2003 budget request for the NIH, based on current law, is \$27,244 million, including VA/HUD appropriated Superfund-related research activities.

The threat of bioterrorism became a reality in the United States with the intentional delivery of anthrax spores through the mail to print media, television, and government offices. The anthrax attacks have dramatized the vulnerability of the United States population to such events. The magnitude of the problem and the gravity of the situation are a reminder of the danger of biological weapons and their potential impact on public health. The importance of meeting this public health challenge is clear. In consultation with the Federal Office of Homeland Security and the HHS Office of Public Health Preparedness, the NIH has developed a FY 2003 budget request that includes a total of \$1,748 million for bioterrorism-related research and infrastructure, an increase of \$1,473 million over FY 2002.

To expand and build on existing programs, the NIH has developed a comprehensive program designed to sustain research aimed at developing biomedical tools to detect, prevent, and treat infection by biological agents that could serve as potential weapons. In FY 2003, NIH estimates it will fund \$977 million for bioterrorism research activities, to continue existing bioterrorism-related programs, and initiate new ones to accomplish the following milestones:

- Establish the first four to seven Extramural Centers of Excellence for Bioterrorism and Emerging Infections. It is estimated that ten such centers will be established over the next several years. These centers will be based regionally and will form the heart of such extramural research activities in their geographical areas. Each center will provide support to researchers by making available specialized equipment and tools, including biosafety level 3 and/or 4 laboratories; providing specialized knowledge and expert advice; and conducting specialized training.

- Conduct genomic sequencing and annotation of six to ten microbial pathogens.
- Launch challenge grants to industry and academia to attract their long-term interest and support.
- Broaden the support for clinical trials of next-generation vaccines and therapeutic agents through expansion of the Vaccine Trial Evaluation Units (VTEU), specialized laboratory support, and regulatory/monitoring oversight of clinical trials.
- Complete Phase II and start Phase III clinical trials for next-generation smallpox vaccines.
- Conduct Phase I/II clinical trials of next-generation anthrax vaccines.

In the FY 2003 President's Budget, \$250 million is requested for anticipated procurement of anthrax vaccines currently under development and testing.

Progress in the fight against bioterrorism will require support for secure and modernized physical infrastructure. The FY 2003 President's budget request seeks to expand the use of existing construction grant authority to allow the National Institute of Allergy and Infectious Diseases (NIAID) to initiate a \$150 million program for construction/renovation of biosafety level 3 and 4 laboratories at these new Extramural Centers of Excellence for Bioterrorism and Emerging Infections. A total of \$185 million is included in the Buildings and Facilities (B&F) budget request for FY 2003 to construct a biosafety level 4 laboratory on NIH property at Ft. Detrick, MD (\$105 million), and to ensure the physical security of existing NIH laboratories (\$80 million).

The FY 2003 President's budget request will provide \$186 million for the Center for Bioterrorism and Emerging Infections--new laboratory space on the NIH Bethesda campus dedicated to the study of select infectious agents. This new research facility will provide a focus for rapid response programs dealing with select infectious agents that may be used as weapons of bioterrorism and with other emerging infections. The Center will also consolidate existing related research currently spread among different locations on the NIH campus and thereby, better facilitate scientific collaborations. Consolidation will also improve the physical security of these programs and the materials being studied, since access to all laboratory and animal facilities will be contained in one facility built with the state-of-the-art engineering needed to handle these agents. All laboratory areas in the new facility will support work at the BSL-3 level.

The facility will include a vivarium capable of housing large and small animals. Access will be restricted to qualified personnel only. Except for common areas on the entry floor, all areas will be compartmentalized to allow for shutdown and sterilization.

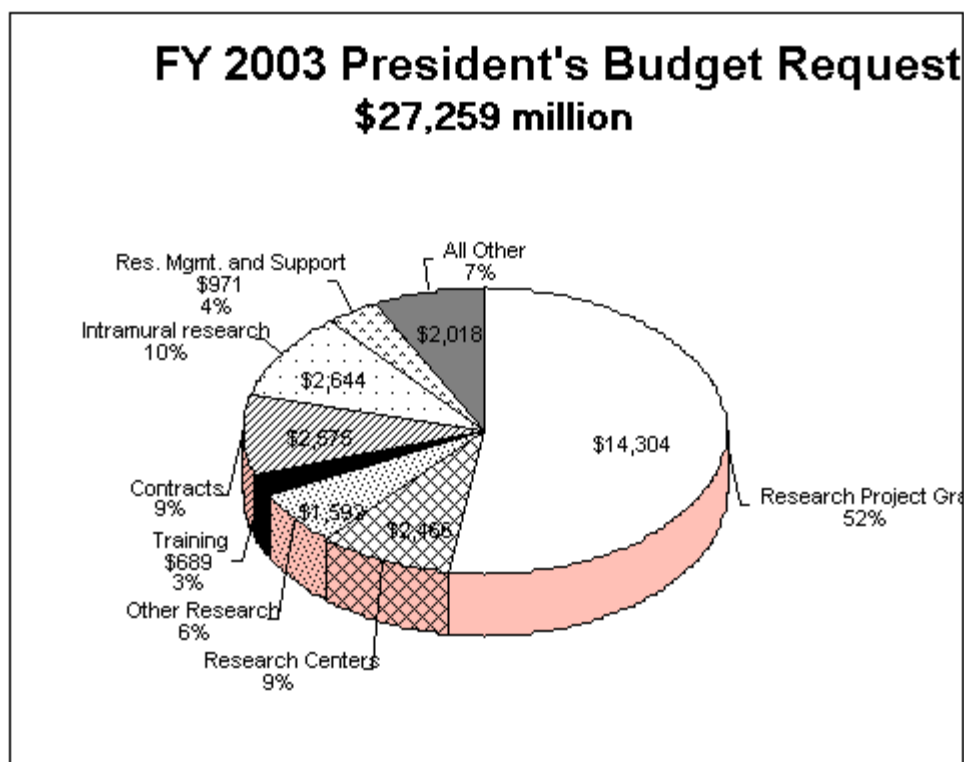
Cancer is the second leading cause of death in the U.S. What we call "cancer" is a hundred-plus distinct diseases, and can affect any organ system. While cancers have several essential attributes in common, each type of cancer has its own unique characteristics that affect how it arises, how it progresses, and how it can be most effectively treated.

With focused efforts and increased resources, NIH will build on past successes and technological breakthroughs to stimulate progress in addressing some of our most difficult questions about cancer. The FY 2003 President's budget request will allow the NIH in total to support an estimated \$5.5 billion in cancer research. Our increased investments in all areas of cancer research will accelerate the pace of cancer research and improve our ability to find better ways to care for those whose lives are touched by cancer.

Support for AIDS research will increase by \$255 million, or 10 percent over the FY 2002 estimate, for a total of \$2,870 million. This amount includes accrued costs for the AIDS research program.

The FY 2003 President's budget request will allow NIH to continue its FY 2002 support of \$100 million for the Global Fund to Fight HIV/AIDS, Malaria, and Tuberculosis, to further the NIH's efforts to prevent and alleviate these diseases.

Mechanism Discussion



NIH is committed to increasing a healthy number of new awards, especially for new and young investigators. The FY 2003 President's budget request allows NIH to build on the scientific momentum of investigator-initiated research and provide such new research opportunities. NIH would fund a total of 9,854 competing Research Project Grants (RPGs) in FY 2003, for \$3,641

million. This represents an increase of 477 competing RPGs over the FY 2002 estimate of 9,377 awards. In FY 2003, total RPGs funded will be 38,038 awards, an increase of 1,408 awards over the FY 2002 Estimate of 36,630 awards, the highest annual total ever awarded.

The Fiscal Year 2003 President's budget request provides average cost increases for competing RPGs equal to the NIH Biomedical Research and Development Price Index (BRDPI), estimated at 4.0 percent. The apparent increase of 7.2 percent in average costs for total competing RPGs from FY 2002 to FY 2003 results from the cycling of unusually expensive noncompeting grants for AIDS research in FY 2002 into competing status in FY 2003 supported by the National Institute of Allergy and Infectious Diseases (NIAID), as well as the funding of expensive bioterrorism-related challenge grants in FY 2003. Noncompeting RPGs will be funded at committed levels which include increases for recurring direct costs of 3 percent on average.

NIH is in the process of analyzing whether there are grant and contract programs for which it is appropriate to expand the strategy of full funding the total costs to maximize management and budgetary flexibility. Therefore, the mechanism table included in the FY 2003 Budget does not assume full funding of any awards, but appropriations language is included in the budget that will allow for the full funding of NIH grants. Once this analysis is complete, NIH will inform Congress of its findings, which will be reflected in the final FY 2003 Operating Plan.

Research Centers increase by \$339 million (16 percent) in the FY 2003 President's budget request. Included in this amount is an increase of \$25 million, for a total of \$185 million in support for the Institutional Development Award (IDeA) program. An additional \$14 million is provided to the National Center for Minority Health and Health Disparities, to increase the Centers of Excellence Endowment program to \$45 million in FY 2003.

The FY 2003 President's budget request will support 17,014 full-time training positions (FTTPs), an increase of 305 FTTPs over the FY 2002 Estimate. Funding will provide an increase of 4 percent for pre-doctoral and post-doctoral stipends for NRSA trainees. This will permit NIH to recruit and retain the best and brightest in medical research careers.

Intramural Research increases by 15 percent over the FY 2002 estimate, with most ICs increasing by 9 percent. The NIAID and NCI increase by 52 percent and 11 percent respectively, as a result of the large increases in bioterrorism and cancer research.

The Research Management and Support (RMS) activity is vital if NIH is to manage its program resources efficiently and effectively. The RMS activity is used by the NIH to sustain, guide and monitor extramural and intramural research activities of the Institutes. To effectively plan and direct its research portfolio, the NIH relies on scientific program managers to develop scientific programs and ensure that the best scientific opportunities and emerging public health priorities are funded. Information technology (IT) systems and expert staff effectively provide health information programs for the public and health professionals. Administrative staff and IT resources are also utilized to ensure proper stewardship of public resources. This activity increases by 17 percent in total in FY 2003. All Institutes and Centers except the National Cancer Institute (NCI) and the NIAID increase by 9 percent over the FY 2002 estimate. The NCI, and in particular, the NIAID are requesting increased resources in the RMS budget activity to effectively manage their large program increases.

The FY 2003 President's budget request provides \$240 million for extramural construction awards. Of this amount, \$150 million will be targeted towards expanding the ability of researchers to access high-containment research facilities (with laboratories of biosafety 3 and 4) by providing construction grants for the renovation or construction of these facilities. In FY 2003, the National Center for Minority Health and Health Disparities will also support construction grant awards. Finally, \$77 million is requested for extramural construction in the National Center for Research Resources.

The FY 2003 President's budget request provides a total of \$315 million for the National Library of Medicine, an increase of 12% over the FY 2002 estimate. Included in this amount is \$10 million to expand programs of the National Center for Biotechnology Information.

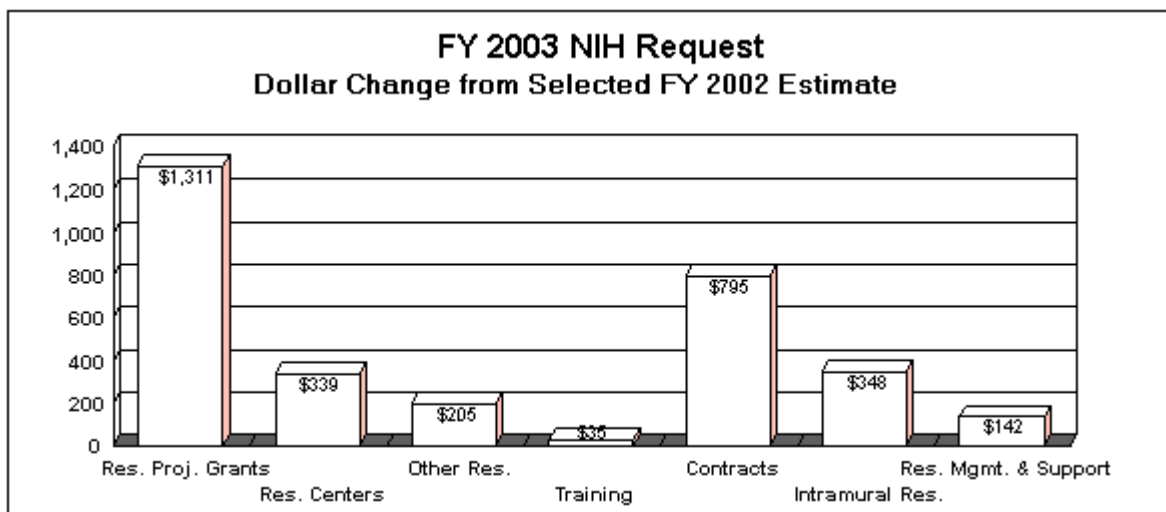
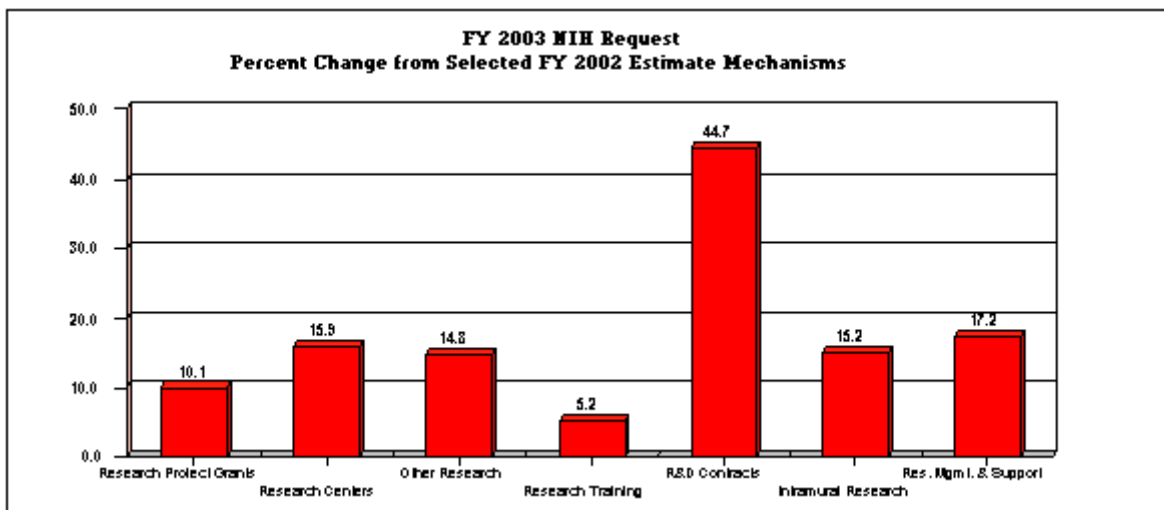
In the FY 2003 President's budget, Buildings and Facilities (B&F) would be funded at \$633 million. This increase will allow the NIH to fulfill its commitment to integrating neuroscience research in the John Edward Porter Neuroscience Research Center (NRC), maintain responsible funding support for the ongoing essential safety, renovation and repair, and related projects that are vital to proper stewardship of the entire portfolio of real property assets, continue with the integration of the new CRC into old Building 10, increase the physical security of NIH facilities, and to construct high containment facilities on the Bethesda Campus and at Ft. Detrick to support bioterrorism research.

The B&F budget request will provide \$168 million to complete the second and last phase of the NRC. The NRC is designed and will be equipped to support high-priority research initiatives using innovative strategies in neurobiology, neuroimaging, and bio-informatics to better describe the link between biochemistry and behavior, to elucidate the nerve cell degenerative processes, and to explore other lines of inquiry that are emerging from the genetic mapping of the brain.

In FY 2003, \$80 million is requested for improvements to the physical security program that will bolster NIH's ability to provide a safe and secure environment for the conduct of the NIH mission on its sites. The specific improvements are planned to enable the NIH to effectively and rationally maintain operations at the full range of federal "alert levels" as necessary.

A major portion of the physical improvements will help to manage and control access to the NIH campus and to campus buildings. Complementing a perimeter fence which is provided through FY 2002 funding, this request includes: a visitor center for welcoming and screening visitors and issuing visitor passes that will also operate as the center for campus-wide transportation services; the construction of the infrastructure to manage and screen deliveries of scientific and other equipment to NIH facilities in the DC metro region; completion of a campus loop road necessary for effective emergency response and proper internal circulation of a large volume of commercial and employee vehicles; security enhancements to specific buildings; and improvements to the information technology infrastructure. Smaller scale, similar projects for the Rocky Mountain Laboratory are also included in this request.

While NIH's facilities construction dollars are requested in NIH, the budget proposes to transfer these funds, along with those for other HHS construction projects, to the Health Facilities Construction and Management Fund in the Office of the Secretary for oversight by the Office of the Assistant Secretary for Administration and Management. This reflects HHS's commitment to improve HHS-wide capital planning.



Other Key Issues

The NIH request includes funding to support Departmental efforts to improve the HHS Information Technology Enterprise Infrastructure. The request includes funds to support an enterprise approach to investing in key information technology infrastructure such as security and network modernization. These investments will enable HHS programs to carryout their missions more securely and at a lower cost. Agency funds will be combined with resources in the Information Technology Security and Innovation Fund to promote collaboration in planning and

project management and to achieve common goals such as secure and reliable communication and lower costs for the purchase and maintenance of hardware and software.

The Unified Financial Management System (UFMS) will be implemented to replace five legacy accounting systems currently used across the Operating Divisions. The UFMS will integrate the Department's financial management structure and provide HHS leaders with a more timely and coordinated view of critical financial management information, including more accurate assessments of the cost of HHS programs. It will also promote the consolidation of accounting operations and thereby reduce substantially the cost of providing accounting services throughout HHS. Similarly, UFMS, by generating timely, reliable and consistent financial information, will enable OPDIV Heads and program administrators to make more timely and informed decisions regarding their operations.

The Extramural Clinical Research and the Pediatric Research Loan Repayment Programs are trans-NIH programs supported by nearly all the ICs. The FY 2003 President's budget request doubles this program by providing \$28 million over the FY 2002 estimate. These programs will help to increase the number of outstanding investigators in Clinical and Pediatric Research in the future, with a goal of supporting pediatric researchers with 15-20 percent of these awards.

In the FY 2003 President's budget request, a total of \$49 million is directed towards collaborative research projects with the Department of Defense, including development of an HIV/AIDS vaccine, research into the use of free electron lasers for surgical debridement, and research into radiation treatment research.

In addition to resources requested in the FY 2003 President's budget, Section 931 of the Benefits Improvement and Protection Act of 2000 increased mandatory funding to the Secretary, HHS for research into the prevention and cure of Type I diabetes from \$30 million to \$100 million a year beginning in FY 2001. NIH has developed an interagency research plan that calls for NIH to utilize \$97 million of these funds for expanded efforts in identifying genetic and environmental causes of type 1 diabetes; preventing or reversing the disease by developing cell replacement therapies; reducing or preventing hypoglycemia; preventing or reducing complications in patients with type 1 diabetes; and attracting new talent to this field of research.

	FY 2001	FY 2002	FY 2003	Change
FTEs	16,513	17,443	17,696	+225
CRADA FTEs 1/	12	28	28	0
Total FTE	16,525	17,471	17,696	225

1/ CRADA FTEs are supported by Cooperative Research and Development Agreements

NIH trains and retains a continuing supply of personnel that are prepared to understand the implications of current discoveries to future research opportunities. Staff roles include ensuring the best possible stewardship of NIH resources, disseminating information on NIH research advances to health professionals and the general public, and providing expertise in developing new programs, such as the major expansion in bioterrorism research. Full-Time Equivalent (FTE) positions requested for FY 2003 are consistent with the increases of approximately 15 percent over the FY 2002 Estimate in the Intramural Research program and 17 percent in the Research Management and Support program.